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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

August 31, 1999

MEMORANDUM

SUBJECT: TPTH: Response to EPA Transmittal of the Preliminary HED Risk Assesssment for TPTH, PC Code # 083601, DP Barcode: D258270.

FROM: Sarah Levy, Chemist 8/31/99
and
John Doherty, Toxicologist 8/31/99
Reregistration Branch 3
Health Effects Division (7509C)

THROUGH: Steve Knizner, Branch Senior Scientist
Reregistration Branch 3
Health Effects Division (7509C)

TO: Loan Phan, Chemical Review Manager
Special Review and Registration Division (7508C)

Responses to the HED TPTH Preliminary Risk Assessment, dated May 14, 1999, were received from Landis International consultants in their memo on behalf of the TPTH Task Force. The comments received were summarized in the Landis memos dated July 28, 1999 and August 13, 1999.

In summary, HED has not received any additional data from the registrant that would alter the decisions made by the Hazard Identification Assessment Review Committee, the FQPA Safety Factory Committee or the Carcinogencity Peer Review Committee concerning dose/endpoints or uncertainty/safety factors selected or the carcinogencity classification of TPTH.

HED has revised the acute and chronic (non-cancer and cancer) dietary exposure risk assessments in concurrence with the review and evaluation of the registrant's submission of acute and chronic dietary exposure and risk analyses (S. Levy, D257154, 8/20/99, MRID #44852101). Furthermore, HED has also revised the Residue Chemistry Chapter (C. Eiden,

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D255118, 08/25/99) in which new acute and chronic anticipated residues (ARs), processing factors and percent crop treated (%CT) information for meat and milk (See S. Levy, D257154, 8/20/99) of TPTH were given.

Acute dietary exposure and risk estimates (from food exposure only) are below HED's level of concern. The most highly exposed population subgroup was females 20+ years old, not pregnant, not nursing, with **34%** of the acute PAD (aPAD) occupied.

Chronic (non-cancer) dietary exposure and risk estimates (from food exposure only) are significantly below HED's level of concern. The most highly exposed population subgroup was children, 1-6 years old, with **4%** of the chronic PAD (cPAD) consumed.

Estimated carcinogenic risk (from food exposure only) for TPTH is in the range that the Agency considers negligible for excess lifetime cancer risk (i.e. 1 x 10^{-6}).

Please see individual sections below for details of Landis' comments and HED's responses.

TOXICOLOGY

A. Acute Risk Assessment

The issue concerns the incorporation of an additional 3X safety factor for FQPA based on the possible potential for immunotoxic effects following an acute dose. Since this concerns FQPA, this issue will be discussed below along with other FQPA issues.

B. Chronic (non-cancer) Risk Assessment

The registrant's issue concerns an objection related to inclusion of an additional 3x uncertainty factor based on instability of the test material in the diet and because there were deaths at the LOAEL which was considered a dose level that was close to the NOAEL.

HED based its concern for instability of the test material in the diet because there was no analytical report for the 1970 study (MRID No.: 099050) and in the 1989 chronic feeding study in rats (MRID No.: 41085702) the analytical values ranged from 79.6 to 115.7% of the nominal doses and homogeneity was from -14% to +17% with one occasion ranging from -29% to +52%. The recommendation for inclusion of an extra 3x uncertainty factor was recommended by the previous RfD assessment and sustained by the most recent HIARC review (November 13, 1998). Although the toxicologist in his review (DER) implied that the dietary analysis would not compromise the integrity of the study, the HIARC, as a peer review committee, has the final say and can overrule the conclusions in the DER.

The comment provided by the registrant that the tissue analysis for tin in the chronic feeding study does not convince HED that TPTH was stable in the test diets or had more acceptable

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homogeneity and constant concentration. There were not enough assessments for tissue tin levels over the course of the experiment.

The issue of mortality at the low dose in the 1989 chronic feeding rat study being a factor in determining that an additional 3x uncertainty factor be used for the chronic RfD setting is typical of the way HIARC assigns additional uncertainty factors to a LOAEL since a NOAEL is not established in the study. The possible association with the increase in deaths being related to the pituitary tumors does not negate the call for this additional uncertainty factor for the chronic RfD.

HED considers that the registrant has interpreted the term "high degree of confidence in the existing database" for their own convenience. It was apparently HED's intention to say that the available data lend a high degree of confidence to the assessment of developmental toxicity and carcinogenicity. In addition, indications of immunotoxicity were noted in multiple studies and in different species to lend a high degree of confidence that TPTH potentially affects the immune system. The statement that there is a high degree of confidence in the database has no bearing on the selection of the uncertainty factors for individual risk assessments. The uncertainty factors relate to the severity of the toxicity at the LOAEL (i.e. deaths) when there is no NOAEL for the study.

Although HED is aware that there is no evidence that suggests that there will be effects on the immune system following acute dosing and that the registrant asserts that immunotoxicity responses come after repeated dosing in older animals, there is still a potential for TPTH to affect the immune system in the developing fetus.

C. Chronic (cancer) Risk Assessment

The determination of the carcinogenicity classification of TPTH was set by the Carcinogenicity Peer Review Committee and verified in separate meetings following a Science Advisory Panel (SAP) meeting on TPTH. Current HED policy does not provide that a chemical will be revisited by the carcinogenicity peer review committee unless a new carcinogenicity study or other significant new data have been submitted. The current classification will remain unless new data are presented that will warrant a revisit to the peer review committee and the committee decides to change the classification.

It should be noted that the issues of MTD and the spontaneous occurrence of each tumor type were considered in the original peer review of TPTH. In the case of TPTH, there are three tumor types in question and the B classification is related to more than one tumor type in more than one sex and in two different species. Thus, although the logic presented in Dr. Landis's letter for reclassifying each tumor type may have some merit, the same logic does not necessarily apply when there are multiple tumor types.

D. FQPA Safety Factor

Acute Dietary 3X

The FQPA Safety Factor Committee recommended that the 10X safety factor be reduced to 3X for the acute dietary exposure (December 17, 1998). The 3x factor was applied since there are questions concerning the potential effects of TPTH on the development of the immune system in fetal and neonatal rats, (i.e., uncertainty). Although there is no consensus among toxicologists that immunotoxicity manifestations are derived from a single exposure, it is the intention of the HIARC that the requested developmental immunotoxicity study will help to address a possible concern for such an effect. It should be noted that the FQPA safety factors are applied when there is an absence of data the FQPA committee considers critical to understanding a potential effect. TPTH will be reviewed by the FQPA committee upon receipt of the review of the developmental immunotoxicity study.

Chronic Dietary 3X

The FQPA committee recommended that the 10X safety factor be retained for TPTH for chronic dietary exposure. This was based primarily on the indications in the rat multi generation reproduction study that the pups showed toxicity at dose levels lower than the parental animals. The registrant states that it is questionable that there was actually toxicity in the pups at a lower dose than in the adults but does not provide convincing data to demonstrate otherwise. Thus, until there is a more convincing demonstration that the pups are not demonstrating indications of toxicity at a lower dose than the parental animals, the rat multi generation reproduction study serves as a basis for retaining the 10 X FQPA safety factor.

The FQPA committee also identified possible effects on the endocrine system as support for retaining the 10X FQPA factor.

There was no specific reason stated in the FQPA report indicating why immunotoxicity effects of TPTH are included in the justification for retaining the 10X FQPA factor. However, the above two effects of TPTH are the major reasons for retaining the 10 X factor.

The issue of the developmental immunotoxicity study is discussed in the following section.

E. Requirement for a Developmental Immunotoxicity Study

Although there are no current guidelines for a developmental immunotoxicity study, the registrant was asked to devise a protocol for this study. Since the chronic RfD is based on potential for immunotoxicity and because one of the critical factors in the LOAEL in the rat multi generation reproduction study included an adverse effect on the spleen and spleen effects appear to be a constant finding in several studies with TPTH, it is considered prudent to assess for potential effects on the developing immune system in the proposed developmental

immunotoxicity study.

In the protocol for this study, the dosing should follow the current protocol for a developmental neurotoxicity study. The registrant will be expected to consult with the appropriate experts in immunotoxicity and select the most appropriate strain of rat, blood and bone marrow and other parameters associated with the immune system to be assessed for, as well as to select an appropriate test to determine if the exposed pups are more susceptible to infection.
HED is aware that there will be no historical control data or established guidance for evaluation of the responses and their interpretation. The proposed study, however, is still considered to be a meaningful insight into the possible potential for TPTH to affect the developing immune system in rats.

F. Subchronic Neurotoxicity

The need for the subchronic neurotoxicity study derives mostly from the fact that TPTH belongs to a class of chemicals (organotins) that are known to be neurotoxic and at least one member of this class (trimethyl tin) is used as positive controls for neurotoxicity studies. After much deliberation related to the facts that neurotoxicity was not seen in the existing data base with rats, mice and dogs, it was still determined that a subchronic neurotoxicity study needed to be provided because the existing studies did not include the more specific assessments of FOB, motor activity and neuropathology parameters.

DIETARY

G. Dietary Risk Assessment

The registrant responds that there is great disparity between HED's and NOVIGEN's dietary risk assessments. The preliminary judgement is that the greatest disparity between the two documents is not the toxicity endpoints used, but rather in how a single item the feeding of sugar beet tops, is addressed. The registrant responds that it appears that the Agency's assessment assumes that all beet tops are fed to beef and dairy cattle and that this occurs for twelve months of the year.

The registrant has made a concerted effort to provide documentation on sugar beet leaf feeding practices. An HED Senior Plant Physiologist (Dr. Bernard Schneider) reviewed the TPTH Task Force response to use of sugar beet tops for livestock use, and contacted various USDA Extension Agents in cooperation with USDA-IR-4, performed a literature search, and contacted sugar beet equipment dealers. He and other members of HED met with ChemSAC (7/21 and 8/ 18/99) and decided on the following approach:

HED concurs with the Task Force that sugar beet tops are not available for grazing 12 months of the year. It is more realistic for the **chronic** assessment to assume sugar beet tops would be available for grazing after harvest for up to one month before the field is plowed (1 month

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availability/12 months). Therefore, for the chronic dietary assessment, the percent of sugar beet treated, the percent of cattle that could feed on sugar beet tops, the temporal component, and the percent of sugar beet tops fed was incorporated as "percent of crop treated" (% CT) in the DEEM™ adjustment factor number 2 column in the chronic assessment:

% CT x % US cattle that could graze on sugar beet tops x (1 month availability/12 months) x % sugar beet tops fed =

0.35 (weighted average) x 0.12 x 0.08 x 0.8 = 0.003 %

However, for the **acute** assessment, it is not appropriate to take into account the temporal component or the % sugar beet tops fed because HED is concerned with dietary acute exposure over a short time period, not residues averaged out over a year.

Therefore, for the acute assessment, the %CT and the percent of cattle that could feed on sugar beet tops was incorporated as "percent of crop treated" in the DEEM™ adjustment factor number 2 column in the acute assessment:

% CT x % US cattle that could graze on sugar beet tops =

0.44 (estimated maximum) x 0.12 = 0.05 %

These approaches were used in the revised acute and chronic (non-cancer and cancer) HED analyses (S. Levy, Draft, D258010) for beef cattle, goats, horses and sheep. Note that dairy cattle are not fed sugar beet tops; therefore, this following approach and assumptions were not applied to dairy cattle (milk in DEEM™), nor for pork. For milk, the sugar beet %CT value was used in the adjustment factor #2 column in DEEM™ to refine the residue value (sugar beet pulp has the highest %CT value of all the feed items calculated into the dairy diet). For pork, the potato %CT value was used in the adjustment factor #2 column in DEEM™ to refine the residue value (processed potato culls are the only feed item calculated into the swine diet).

Acute dietary exposure and risk (from food exposure only) are significantly below HED's level of concern. The most highly exposed population subgroup in this analysis was females 20+ years old, not pregnant, not nursing, with **34%** of the acute PAD (aPAD) consumed. Chronic (non-cancer) (from food exposure only) dietary exposure and risk are significantly below HED's level of concern. The most highly exposed population subgroup in this analysis was children, 1-6 years old, with **4%** of the chronic PAD (cPAD) consumed. Estimated carcinogenic risk (from food exposure only) for TPTH is at the level generally considered to be negligible by the Agency (approximately 1 x 10^{-6}).

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SUMMARY

Neither the acute or chronic dietary FQPA 3X or 10X additional safety factors can be removed without resubmitting the issues to the FQPA committee for reconsideration. Because no new toxicity data have been submitted, TPTH will not be taken back to the HIARC or FQPA committees. The requirement for a developmental immunotoxicity study was explicitly requested by the HIARC which was aware of the limitations as indicated by the registrant. Thus, the requirement for this study remains*. The requirement for the subchronic neurotoxicity study also remains since TPTH belongs to a class of chemicals known to be neurotoxic.

The acute and chronic (non-cancer and cancer) dietary (food only) exposure analyses were revised in concurrence with the review and evaluation of the registrant's submission of acute and chronic dietary exposure and risk analyses (S. Levy, D257154, 8/20/99, MRID #44852101) and with the revised Residue Chemistry Chapter (C. Eiden, D255118, 08/25/99) in which new acute and chronic anticipated residues (ARs), processing factors and percent crop treated (%CT) information for meat and milk (See S. Levy, D257154, 8/20/99) were given. The results for both HED's acute and chronic (non-cancer and cancer) dietary (food only) analyses were significantly lower from the results of HED's previous analyses (S. Law, D254712-13, 4/14/99).

*More recently (as per the August 2, 1999 DCI fact sheet), there will be a DCI issued requesting a developmental neurotoxicity studies with TPTH as well as many other chemicals. Therefore, it is advised that the registrant prepare for receipt of this DCI notice.